REMARKS

Upon entry of the present amendment, claims 1 and 4-18 are pending in the present application. Claims 1, 5-13 and 15-18 are under consideration. Claims 4 and 14 have been withdrawn from consideration. In the present amendment, Applicants amend claims 1 and 5-13, and add new claims 15-18 as follows:

Applicants amend claims 1, 5, 6, 7, 8, 10, 11 and 12 to recite a "test" cell, tissue or nucleus. Support for this amendment is found in the specification, for example, at page 2, lines 7, 11 and 16. Applicants also amend claim 5 to recite "identifying the differentiation state of a test cell, tissue, or nucleus." Support for this amendment is found, for example, in the specification at page 9, lines 17-18 and 23-26 (discussing identifying an undifferentiated embryonic stem cell).

Applicants amend claims 1 and 5 to recite "wherein the DNA methylation pattern . . . comprises information on the methylation state of CpG at a plurality of gene regions." Applicants also amend claims 6 and 10 to recite "information on the methylation state." Those amendments are supported in the specification, for example, at page 4, lines 19-20 (discussing methylation patterns as "the presence or absence of methylation in CpG sequences"); at page 5, last paragraph (discussing "obtaining information on methylation"), at page 6, lines 17-18 (". . .the state of methylation in several thousand regions of genomic DNA can be analyzed . . ."), and at page 9, last paragraph (discussing "a plurality of spots").

Applicants also amend claim 1 to recite "obtaining a cell-, tissue-, or nucleus-specific DNA methylation pattern for at least one known type of cell, tissue, or nucleus." Claim 5 is amended to recite analogous language for a differentiation state-specific DNA methylation

pattern. Support for these amendments is found in the specification, for example, at page 3, lines 6-10 and figures 3-5, at page 19, lines 14-18 (describing the "cell/tissue-specific methylation patterns" of 167 gene regions and stating that "it is possible to specify the type of a cell or tissue by analyzing the methylation pattern thereof . . ."), and at page 19, lines 3-13 and figure 4 (describing methylation patterns [e.g., "spot patterns"] specific to stem cells at different stages of differentiation, e.g., "embryonic stem cell," "trophoblast stem cell," and "differentiated trophoblast cell").

Applicants also amend claim 1 to recite "wherein the test cell, tissue, or nucleus is identified if the DNA methylation pattern of the test cell, tissue, or nucleus matches the cell-, tissue-, or nucleus-specific DNA methylation pattern." Claim 5 is amended to recite analogous language. Those amendments are supported in the specification, for example, at page 9, first full paragraph and the paragraph bridging pages 9-10 (discussing identifying a test cell by comparing the spot pattern of the test cell with that of a known cell having a specific methylation pattern and identifying the test cell if the spot positions match, e.g., "at position 79, a spot is appearing only in embryonic stem cell [undifferentiated]. . . . Thus, a cell that has obtained a spot at position 79 can be identified as embryonic stem cell [undifferentiated]", page 9, lines 16-18), and page 10, lines 14-16 ("it is possible to specify the type of a cell by comparing the spot pattern obtained from the cell with spot pattern information accumulated in the database . . .").

Applicants add new dependent claims 15 and 16 directed to the obtaining of cell-, tissue-, or nucleus-specific DNA methylation patterns. Claim 15 recites "obtaining a DNA methylation pattern for one or more known type of cell, tissue, or nucleus; . . . and identifying gene regions that are differentially and specifically methylated for the known type of cell, tissue or nucleus." Claim 16 recites "comparing the DNA methylation patterns for more than one known type of cell, tissue or nucleus and determining the methylation state of CpG at the differentially

methylated gene regions. . . thereby obtaining a cell-, tissue-, or nucleus-specific DNA methylation pattern." New dependent claims 17 and 18 are added to recite analogous language for differentiation state-specific DNA methylation patterns. These amendments are supported, for example, in the specification at page 4, lines 11-29 (explaining a hypothetical example analyzing the methylation patterns of eight genes in three different cell types); and page 8, lines 18-27 and the paragraph bridging pages 8 and 9 (describing methylation patterns from eight cell types and the selection of spots whose "appearance varied depending on the types of cells or tissues tested" for further analysis).

Applicants amend claims 7 and 11 to recite "determining nucleotide sequence information for differentially methylated gene regions." These amendments are supported in the specification, for example, at page 19, lines 23-30 (discussing detecting "difference in methylation state in gene regions," and identifying the nucleotide sequences of genes having differences in methylation patterns).

Applicants also amend claims 9 and 13 to delete "analyzed" and recite "obtained," which has antecedent basis in claims 5 and 1, respectively.

Thus, the foregoing amendments do not add new matter.

Applicants also respectfully request that the Examiner initial the Form PTO-1449, which was submitted in a Supplemental Information Disclosure Statement dated May 24, 2004, to indicate that the listed documents have been considered. In addition, Applicants respectfully request that the Examiner initial the foreign patent document, document number WO 99/28498, cited in the Information Disclosure Statement dated April 11, 2002, to indicate that this document has been considered.

I. Rejection of Claims 1, 5, 7, and 11 Under 35 U.S.C. § 102(b)

The Office rejected claims 1, 5, 7, and 11 under 35 U.S.C. 102(b) as allegedly anticipated by U.S. Patent Number 5,871,917, issued February 16, 1999, to Duffy. Because Duffy fails to teach each and every element of the claims, this rejection is respectfully traversed.

The Examiner states that "Duffy determines a plurality of sites of differential methylation in the examples at columns 21-28 which is all that is required by the instant claims." Advisory Action at 2. Independent claims 1 and 5, however, recite obtaining a DNA methylation pattern comprising "information on the methylation state of CpG at a plurality of gene regions. . . ." Duffy does not discuss obtaining a DNA methylation pattern comprising "information on the methylation state of CpG at a plurality of gene regions. . . ." Indeed, the invention of Duffy "is directed to a method of detecting differential methylation at *CpNpG* sequences. . . ." *See* Duffy at col. 2, lines 8-10 (emphasis added); *see also* Summary of the Invention, col. 3, lines 5-13 and lines 41-43; col. 10, lines 12-14; col. 16, lines 62-64; col. 18, line 66 through col. 19, line 2 (repeatedly discussing the "CNG triplet"); and col. 24, line 64 through col. 28, line 32 (providing examples directed to the methylation of CpCpGp, which is methylated on the external cytosine, col. 25, lines 41-42).

Furthermore, independent claims 1 and 5 also recite "identifying a test cell, tissue, or nucleus comprising . . . comparing the DNA methylation pattern for the test cell, tissue, or nucleus with the [cell-, tissue-, or nucleus-specific or differentiation state-specific] DNA methylation pattern, wherein the test cell, tissue, or nucleus is identified if the DNA methylation pattern of the test cell, tissue, or nucleus matches the [cell-, tissue-, or nucleus-specific or differentiation state-specific] DNA methylation pattern." Nowhere does Duffy teach "identifying a test cell, tissue, or nucleus comprising . . . comparing the DNA methylation pattern for the test cell, tissue, or nucleus with the [cell-, tissue-, or nucleus-specific or differentiation

state-specific] DNA methylation pattern, wherein the test cell, tissue, or nucleus is identified if the DNA methylation pattern of the test cell, tissue, or nucleus matches the [cell-, tissue-, or nucleus-specific or differentiation state-specific] DNA methylation pattern."

To elaborate, the "[cell-, tissue-, or nucleus-specific or differentiation state-specific] DNA methylation pattern" of the instant claims is a cell-, tissue-, or nucleus-specific [or differentiation state-specific] DNA methylation pattern sufficiently unique to permit identification of an unknown cell type or a cell of unknown differentiation state (e.g., a cell of interest) by comparing the DNA methylation patterns for the unknown test cell with those that are cell-, tissue-, or nucleus-specific or differentiation state-specific and identifying the unknown cell type or differentiation state if the test cell's DNA methylation pattern matches a cell-, tissue-, or nucleus-specific or differentiation state-specific pattern. *See* specification, page 2, lines 28-29 (". . . each cell type has its own methylation patterns. . . . "), page 3, lines 28-30 (". . . there exist unique genomic DNA methylation patterns depending on the types of cells"), and page 6, lines 15-17 ("[b]y producing such . . . patterns for a cell of interest and for cells to be used for comparison and then comparing those . . . patterns, the cell of interest is identified").

In contrast, the cell-type specific methylation patterns discussed in Duffy are not sufficiently unique to permit identification of an unknown cell type or a cell of unknown differentiation state by comparing the DNA methylation patterns for the unknown test cell with those that are cell-, tissue-, or nucleus-specific or differentiation state-specific and identifying the unknown cell type or differentiation state if the test cell's DNA methylation pattern matches a cell-, tissue-, or nucleus-specific or differentiation state-specific pattern. For example, Duffy identifies three gene regions (designated BR50, BR104, and BR254, col. 26, lines 1-2) from human breast cancer samples for DNA methylation studies as discussed in the examples in col. 26-28. Although Duffy shows that these three gene regions are differentially methylated in some

breast tumors as compared to normal breast tissue from the same individual, col. 26, lines 1-33, the methylation pattern of these gene regions is not specific enough to breast tumor cells to permit identification of an unknown tumor cell as a breast tumor cell. This can be seen from the data showing that DNA from only five of ten and ten of 16 breast tumor cell samples, respectively, shared the same methylation pattern as the "parental patient," col. 26, lines 40-46 and 48-50. Thus, the methylation pattern of the BR50, BR104, and BR254 gene regions is not sufficiently "unique" to breast tumor cells since different breast tumor DNA samples from different patients yielded different methylation patterns. Therefore, unlike the instant invention, Duffy does not teach "a method of identifying a test cell, tissue, or nucleus comprising . . . comparing the DNA methylation pattern for the test cell, tissue, or nucleus with the [cell-, tissue-, or nucleus-specific or differentiation state-specific] DNA methylation pattern, wherein the test cell, tissue, or nucleus is identified if the DNA methylation pattern of the test cell, tissue, or nucleus matches the [cell-, tissue-, or nucleus-specific or differentiation state-specific] DNA methylation pattern."

Additional examples in Duffy further demonstrate that the BR50, BR104 and BR254 gene regions are not sufficiently unique to permit identification of an unknown cell type. *See* col. 27, lines 17-18 and 27-30 (showing that the BR50 and BR254 gene regions are differentially methylated in ovarian tumor cell DNA samples as compared to normal DNA samples, and that DNA from only five of eight and four of 11, respectively, ovarian tumor cell samples shared the same methylation pattern as the "parental [breast cancer] patient"). Since some of the ovarian tumor cell DNA samples yielded the same methylation pattern with the BR50 and BR254 probes as some of the breast cancer cell DNA, and since not all tumor DNA samples yielded the same result with these probes, then knowing the methylation state of the BR50 and BR254 gene

regions is not sufficient to identify a cell as a particular type (e.g., breast or ovarian) nor to identify a cell as normal or cancerous.

Furthermore, Duffy discusses how the BR104 probe did not detect a difference in hybridization patterns between ovarian tumor DNA and normal ovarian DNA samples and concludes that "the BR104 probe was detecting a tissue-specific hypomethylation event." Col. 27, lines24-26. Similarly, Duffy found no difference in methylation patterns between colon tumor DNA and normal colon DNA samples using the BR50 and BR104 probes and concludes that, in colon DNA, these probes detect a "tissue-specific hypomethylation event." Col. 28, lines 13-17. However, detection of a tissue-specific hypomethylation event does not permit identification of an unknown cell type by comparing the DNA methylation pattern of the unknown cell with that of a cell-, tissue-, or nucleus-specific or differentiation state-specific DNA methylation pattern. For example, if a DNA sample of unknown origin yields a hypomethylation event detected by probe BR104, the data from Duffy provides that this unknown DNA sample could be from a breast tumor cell, an ovarian tumor cell, a normal ovarian cell, a colon tumor cell or a normal colon cell since Duffy shows that this probe detects a hypomethylation event in these five different cell types. Likewise, if a DNA sample of unknown origin yields a hypomethylation event detected by probe BR50 and BR104 combined, the data from Duffy provides that this unknown could be a breast tumor cell, a colon tumor cell or a normal colon cell since Duffy shows that these probes detect a hypomethylation event in these three different cell types. Finally, Duffy teaches that probe BR254 shows a differential methylation pattern when comparing colon tumor DNA with normal colon DNA; however, the pattern observed is exactly opposite of that seen in breast and ovarian cancer patients. Col. 28, lines 19-27. Duffy thus shows that BR254 detects a hypomethylation event in breast and ovarian cancer, but a hypermethylation event in colon cancer. Thus, if a DNA sample of unknown origin

yielded a hypermethylation event detected by probe BR254, Duffy provides that this unknown could be a normal breast cell, a normal ovarian cell, or a colon cancer cell since Duffy showed that this probe detected hypermethylated DNA in all three of these cell types. Therefore, Duffy does not teach the use of methylation patterns to identify the cell type of an unknown cell, or its differentiation state, by comparing the DNA methylation patterns for the unknown test cell with those that are cell-, tissue-, or nucleus-specific or differentiation state-specific and identifying the unknown cell type or differentiation state if the test cell's DNA methylation pattern matches a cell-, tissue-, or nucleus-specific or differentiation state-specific pattern.

The Examiner also states that "[t]he proposed amendment is vague in that the proposed new limitation 'a plurality of gene regions' could mean either regions within a single gene or a plurality of different genes." Advisory Action at 2. The term "plurality of gene regions" should be given its broadest interpretation, encompassing a plurality of gene regions corresponding to a single gene or a plurality of gene regions corresponding to different genes. *See* M.P.E.P. § 2111 at 2100-46 (8th ed. rev. 1 Feb. 2003).

In view of the foregoing, Applicants respectfully request withdrawal of the rejection of claims 1, 5, 7, and 11 under 35 U.S.C. § 102(b).

II. Rejection of Claims 1, 5-7, 9-11, and 13 under 35 U.S.C. § 102(b)

The Office rejected claims 1, 5-7, 9-11, and 13 under 35 U.S.C. § 102(b) as allegedly anticipated by Zhu et al., Proc. Nat'l Acad. Sci. USA 96:8058-8063 (1999). Because Zhu fails to teach each and every element of the claims, this rejection is respectfully traversed.

Independent claims 1 and 5 recite "identifying a test cell, tissue, or nucleus comprising . . . comparing the DNA methylation pattern for the test cell, tissue, or nucleus with the [cell-, tissue-, or nucleus-specific or differentiation state-specific] DNA methylation pattern, wherein

the test cell, tissue, or nucleus is identified if the DNA methylation pattern of the test cell, tissue, or nucleus matches the [cell-, tissue-, or nucleus-specific or differentiation state-specific] DNA methylation pattern." Zhu does not show "identifying a test cell, tissue, or nucleus comprising . . . comparing the DNA methylation pattern for the test cell, tissue, or nucleus with the [cell-, tissue-, or nucleus-specific or differentiation state-specific] DNA methylation pattern, wherein the test cell, tissue, or nucleus is identified if the DNA methylation pattern of the test cell, tissue, or nucleus matches the [cell-, tissue-, or nucleus-specific or differentiation state-specific] DNA methylation pattern." Rather, Zhu merely analyzes DNA methylation in various T cell clones derived from the peripheral blood lymphocytes of one individual and shows that, in three of the T cell clones, certain gene regions demonstrate methylation heterogeneity. *See* figure 2 and Table 3. Nowhere does Zhu show "identifying a test cell, tissue, or nucleus comprising . . . comparing the DNA methylation pattern for the test cell, tissue, or nucleus with the [cell-, tissue-, or nucleus-specific or differentiation state-specific] DNA methylation pattern, wherein the test cell, tissue, or nucleus is identified if the DNA methylation pattern of the test cell, tissue, or nucleus matches the [cell-, tissue-, or nucleus-specific or differentiation state-specific] DNA methylation pattern."

In view of the foregoing, Applicants submit that Zhu does not anticipate claims 1 and 5, nor does it anticipate claims 6-7, 9-11, and 13, which ultimately depend from claim 1 or 5. Withdrawal of the rejection of those claims under 35 U.S.C. § 102(b) is respectfully requested.

III. Rejection of Claims 1, 5, 7, 8, 11, and 12 Under 35 U.S.C. § 102(b)

The Office rejected claims 1, 5, 7, 8, 11, and 12 under 35 U.S.C. § 102(b) as allegedly anticipated by Hertz et al., J. Biol. Chem. 274:24232-24240 (1999). Specifically, the Examiner stated that "Hertz et al. shows in the abstract the assay of methylation patterns of genes in several

different mouse embryonic stem cell lines. The differences of methylation patterns in inserted genes are detailed in figures 4-9." Final Action at 4. The examiner also stated that "Hertz compares the methylation state of different cells at a number of different loci." Advisory Action at 2. Because Hertz does not teach each and every element of the claimed invention, Applicants respectfully traverse.

Hertz investigates factors affecting the methylation of foreign DNA after it is experimentally introduced into the genome of embryonic stem cells. Hertz does not show identifying a test cell, tissue, or nucleus comprising "comparing the DNA methylation pattern for the test cell, tissue, or nucleus with the [cell-, tissue-, or nucleus-specific or differentiation state-specific] DNA methylation pattern, wherein the test cell, tissue, or nucleus is identified if the DNA methylation pattern of the test cell, tissue, or nucleus matches the [cell-, tissue-, or nucleus-specific or differentiation state-specific] DNA methylation pattern," as recited in the last paragraph of claims 1 and 5. Therefore, Hertz does not anticipate claims 1 and 5, nor does it anticipate claims 7, 8, 11, and 12, which ultimately depend from claim 1 or 5. Withdrawal of the rejection of these claims under 35 U.S.C. § 102(b) is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims. If the Examiner does not consider the application to be allowable, the undersigned requests that, prior to taking action, the Examiner call her at (650) 849-6778 to set up an interview.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account 06-0916.

Respectfully submitted,

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Dated: December 22, 2004

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